National Toxicology Program
Board of Scientific Counselors

May 10, 2010

National Institute of Environmental Health Sciences
Research Triangle Park, NC

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Summary Minutes May 10, 2010
NTP Board of Scientific Counselors

I. Attendees

Members in Attendance

Tracie Bunton, Eicarte LLC
Edward Carney, The Dow Chemical Company
Russell Cattley, Amgen
David Eastmond, University of California
Elaine Faustman, University of Washington
William Janzen, The University of North Carolina at Chapel Hill
Stephen Looney, Medical College of Georgia
Raymond Novak, Wayne State University (Chair)
Ruthann Rudel, Silent Spring Institute
James Sherley, Boston Biomedical Research Institute

Members not in attendance

Janan Eppig, The Jackson Laboratory
Mitzi Nagarkatti, University of South Carolina School of Medicine
Gina Solomon, Natural Resources Defense Council
Justin Teeguarden, Pacific Northwest National Laboratory

National Institute of Environmental Health Sciences (NIEHS) Staff

Eddie Ball
Linda Birnbaum
John Bucher
Matthew Burr
Rajendra Chhabra
Gwen Coleman
Suzanne Fenton
Kembra Howdeshell
Gloria Jahnke
Annette Kirshner
Steven Kleeberger
Robin Mackar
Scott Masten
Retha Newbold
John Pritchard
Andrew Rooney
Robert Sills
Cynthia Smith
William Suk
Kyla Taylor
Kristina Thayer
Raymond Tice
Nigel Walker
Vickie Walker
Lori White
Mary Wolfe

Other Federal Agency Staff

Paul Howard, Food and Drug Administration (FDA)
Mark Toraason, National Institute for Occupational Safety and Health (NIOSH)

Public

Christopher Cordle, Abbott Nutrition
Joseph Manuppello, People for the Ethical Treatment of Animals
Martin Ronis, University of Arkansas for Medical Sciences
Barbara Shane, B. Shane Consulting
Michael Waters, Integrated Laboratory Systems, Inc.
Larry Williams, International Formula Council

II. Introductions and Welcome

The National Toxicology Program (NTP) Board of Scientific Counselors (BSC) met on May 10, 2010, in Rodbell Auditorium, NIEHS, Research Triangle Park, North Carolina. Dr. Raymond Novak served as chair. He welcomed everyone to the meeting and asked the BSC members and attendees to introduce themselves. Dr. Linda Birnbaum, Director of the NIEHS and NTP, acknowledged the full day of important, high profile work ahead, and thanked the BSC members for their service. NTP Associate Director Dr. John Bucher also thanked those in attendance, and stated that given the very full agenda, Dr. Birnbaum and he would forego their usual updates to the BSC, saving those presentations for the June meeting. Dr. Lori White read the conflict of interest statement.

III. Peer Review of Draft NTP Brief on Soy Infant Formula

A. BSC Charge and Background on NTP Level of Concern Conclusions

Dr. Kristina Thayer, Acting Director of the Center for the Evaluation of Risks to Human Reproduction (CERHR), reviewed the charge to the BSC: to determine whether the scientific information cited in the draft NTP Brief on Soy Infant Formula (SIF) (hereafter the draft brief is referred to as the "Draft Brief") is technically correct, clearly stated, and supports the NTP's conclusions regarding the potential for SIF to cause adverse developmental effects. The action requested was: NTP BSC will vote on whether the science cited in the draft NTP Brief on SIF supports the conclusion of *minimal concern* for adverse effects on development in infants who consume SIF.

Dr. Thayer provided background information regarding the rating scales for NTP levels of concern and the weight of evidence for adverse effects used by the NTP to arrive at the conclusions presented in the Draft Brief. She provided the ratings for propylene glycol, bisphenol A (BPA), and di(2-ethylhexyl) phthalate as examples.

B. BSC Discussion

Citing the lack of a definition and serious concerns about the levels of concern approach itself, Dr. Elaine Faustman said she felt that she could not vote on the level of concern conclusions. She expressed doubt that the language in the levels of concern approach is intuitively understandable. She encouraged the NTP to take another look at this approach. She said the weight of evidence approach is consistent with approaches already in use in many places in the world; however, the levels of concern are confusing.

Dr. Birnbaum asked Dr. Faustman whether she had a definition, given her concern about the lack thereof. Dr. Faustman replied that she had specifically defined her concerns in her written review document, and that given the confusion raised by the acknowledged lack of definitions in the levels of concern scale, the entire approach needs more work. Dr. James Sherley said he recognized the role of NTP in informing, not setting, policy, but that getting some response to the levels of concern might help arrive at desired definitions. Dr. Bucher acknowledged that this has been an area CERHR has struggled with over the years. The Draft Brief differs from Technical

Reports issued by NTP; CERHR briefs are more a review and assessment of the world's literature on the topic and a method for communicating about the potential risk to human reproduction and/or development from an environment substance that should be brought to the attention of the public and the regulatory agencies. As such, CERHR's work is not cut-and-dried, and its evaluations follow no particular formula. He said this meeting's discussions would be taken under advisement as work on the program evolves. Dr. Thayer agreed that CERHR had given a great deal of thought to the definitions of the categories, but concluded there was no *a priori* way to do so; the best approach was to be quite transparent about the process. Dr. Faustman reiterated her contention that definitions are essential, and that the current approach is too early for use, diminishing the scientific quality and thoughtfulness of the document.

Dr. Birnbaum thanked Dr. Faustman for her concerns, and reminded the group that even the "weight of evidence" scale is often confusing to policy-makers, who sometimes take the term literally. Thus, she said, the trend with policy-makers is to move more toward understandable terminology than hard numbers.

Ms. Ruthann Rudel mentioned that in her experience some people find the term "minimal concern" to be confusing, being unsure whether it refers to a great deal of data with few concerns, or scarce data with just a few points of concern.

C. Public Comments

Dr. Larry Williams, Medical Director of the Abbott Nutrition Division, presented the International Formula Council's (IFC) assessment of the Draft Brief. The IFC found:

- The "possible concern" assessment is not scientifically justified—it is too vague, and is interpreted by the lay public as "a real and serious risk."
- The unbalanced evaluation will unnecessarily alarm parents and potentially put infant health at risk, by causing parents to switch to other methods when SIF is clearly medically indicated.
- The assessment is based only on misrepresented animal data.
- The brief does not provide "clear, balanced, and scientifically sound information"—Dr. Williams cited several misgivings, particularly emphasizing the 50-year, 25-million-infant safety track record of SIF without detection of the adverse symptoms seen in many of the animal experiments.
- Written comments and oral testimony since 2006 from external scientific sources have not been considered by NTP, including questions regarding the appropriateness of rodent and primate animal models, the advantage of porcine models, and several other scientific points.

Dr. Williams said the IFC finds the current NTP research plan to be "more of the same" in animal studies and human trials, and instead recommends that future animal studies employ porcine models fed SIF, along with retrospective human research using the 25 million available subjects in age groups to 50 years.

Mr. Joseph Manuppello, Research Associate, People for the Ethical Treatment of Animals (PETA), related PETA's position that given the long, safe track record of human

SIF use, the continued use of animals in research into SIF cannot be justified, particularly in light of the recognized differences in SIF metabolism between animal species and humans. Instead, he said, carefully designed epidemiological research in humans would be more valuable. He discussed several of the studies cited by NTP in the Draft Brief (e.g. Strom *et al*., D'Aloisio *et al*.), concluding that there were limitations in the studies reporting correlations between SIF and reproductive effects, rendering the significance of the reported associations questionable. He felt that NTP unduly dismissed negative studies in humans. He reported that PETA felt that the question answered "possibly" in the Draft Brief (Can SIF or its Isoflavone Contents Adversely Affect Human Development?) should be answered "probably not."

Dr. Martin Ronis, Arkansas Children's Nutrition Center at the University of Arkansas, stated that whole food should be more strongly considered in studies of SIF, in that looking in isolation at dietary components such as genistein can be misleading in terms of estrogenicity. He provided details about a large longitudinal study being conducted at his Center, with 200 breast-fed, 200 milk formula-fed, and 200 SIF-fed infants being followed over the course of six years. He reported the results of a preliminary study comparing estrogen-sensitive reproductive organ size (a marker of estrogenicity) at four months of age in subsets of the three groups in the cohort. The soy-fed group did not differ in reproductive organ size. Dr. Ronis related the limitations cited by the CERHR Expert Panel in their designation of the study as being of limited or no utility, and felt that the study in fact used closely matched groups and reflected the real world of SIF feeding, contrary to the panel's criticisms. He also reported unpublished results from a study in piglets that indicated no negative impact from SIF exposure, as well as data from several gene expression studies that supported the hypothesis that SIF, genistein, and estradiol have distinct expression profiles. He stated his group's conclusions that SIF has no effect on reproductive development in infants, and that SIF/soy protein isolate is not estrogenic.

Dr. Sherley asked Dr. Ronis what the impact would be of not having SIF available. Dr. Ronis replied that it would be seriously adverse, due to the many infants who cannot tolerate cow milk formulas and whose mothers cannot express breast milk. He said there is no concern about SIF among pediatricians, with the American Academy of Pediatrics (AAP) sharing that view, and that in fact there may be health benefits associated with SIF consumption.

Dr. Faustman asked Dr. Ronis for more information about his toxicogenomic studies, whether he had included genistein in them, and if so, whether he saw comparable gene expression patterns with E2. He replied that he was unaware of any study that had done a complete comparison of genistein, soy protein isolate, and estradiol. Dr. Faustman asked for clarification regarding the AAP recommendations. Dr. Ronis said the AAP recommends breast milk, cow milk formula, and SIF, in that order, but does not discourage use of SIF altogether.

Dr. Edward Carney asked why the pig model is considered to be better than other animal models. Dr. Ronis cited a 2005 study by his group, Gu *et al*., concerning isoflavone metabolism following soy protein isolate consumption, comparing infant

humans, neonatal piglets, rats and monkeys. The study found that rodents and monkeys completely convert daidzein to equol, the most biologically active soy isoflavone. There was no evidence of any equol production in either the human infants or the piglets, showing that their metabolism of soy isoflavones is comparable.

Dr. David Eastmond asked about the ongoing longitudinal study, which is still in its early stages. Dr. Ronis replied that the study is five years old, so some of the infant cohort is not five years of age, with most currently between one and two. Dr. Eastmond pointed out that the basis of the grant is unanswered questions regarding SIF consumption, and that the ultimate answers may still be 10-15 years away. Dr. Ronis agreed, and stated that it is important to continue to study SIFs, but that, although his group does not believe there is any particular evidence of reproductive toxicity, potential effects in immune development, drug metabolism and lipid homeostasis, some of which may actually be beneficial, are worth studying.

Dr. Sherley asked Dr. Ronis about the history of case reports connected with SIF consumption, relative to the overall safety record. Dr. Ronis replied that there are some anecdotal case reports in the record, which largely deal with allergic reactions, intolerance later in life associated with early consumption of soy protein, and with potential thyroid effects, but the reports are very scattered.

Dr. Birnbaum and Dr. Thayer asked Dr. Ronis about data from his study regarding circulating blood levels of conjugated versus unconjugated genistein in the infants. He said the data were still incomplete, so he could not comment, but that their data were comparable to that already published by Setchell with respect to total levels of isoflavone.

Dr. Faustman asked Dr. Ronis for his thoughts regarding the wide variability of equol production in infants. He answered that his group has not detected equol production in an infant prior to weaning. He said equol is produced by gut bacteria, and so is likely related to diet in adults, and is sensitive to cultural dietary differences. He agreed that there are technical issues regarding detection of equol, but was confident that his group would have detected it in their cohort if it had been present.

D. Background and Scientific Development of Draft NTP Brief on Soy Infant Formula

Dr. Thayer said SIF has been used since the 1950s to replace or supplement the use of breast milk or cow milk-based formula. SIF contains soy protein isolate at 14-16% by weight. Soy isoflavones with estrogenic activity (“phytoestrogens”) are ranked genistein > daidzein > glycitein in terms of relative abundance in SIF and relative estrogenic activity. The basis for the NTP evaluation is (1) the availability of studies in humans and laboratory animals relevant for an assessment of developmental toxicity, (2) the availability of information on isoflavone exposure in infants fed SIF, (3) public concern, and (4) an update of the 2006 NTP evaluation that was not completed. CERHR convened an expert panel, which met in late 2009, and expressed “minimal concern” for adverse developmental effects in infants fed SIF based on a critical assessment of

relevant human and animal studies of developmental toxicity and the extent of isoflavone exposure in infants fed SIF.

E. Usage and Exposure to Isoflavones in Infants Fed Soy Formula

Dr. Thayer said it is unknown how many infants are fed SIF exclusively, but it comprises approximately 12% of the U.S. infant formula market. The AAP 2008 Policy Statement on SIF states that it can provide nutrition for normal growth and development in term infants, but has limited clinical indications for use. There are two types of isoflavones in SIF (1) the non-biologically active sugar-bound isoflavones genistin, daidzin, and glycitin; and (2) the biologically active aglycone isoflavones genistein, daidzein, glycitein, and equol. *In vitro*, the relative estrogenicity is genistein ≈ equol > daidzein > glycitein. The estimated daily intake of total isoflavones and genistein in infants fed SIF is 2.3-9.3 and 1.3-6.2 mg/kg bw/day, respectively. Blood-based levels of genistein and daidzein in infants fed SIF are at the 75^{th} to 95^{th} percentile compared to adults.

F. BSC Questions and Discussion

Dr. Sherley asked Dr. Thayer how long the high genistein and daidzein levels persist. She responded that for infants, the values shown were the only ones available, but that for adults the half-life is typically 6-7 hours. Dr. Faustman questioned whether samples were being taken from infants too soon after feeding. Dr. Thayer agreed that taking the samples 30-120 minutes after feeding might not represent a maximum level. Dr. Faustman asked whether there were comparable values available for equol production in infants. Dr. Thayer said according to the Setchell and Hoi studies, equol is detectable in infants, but they are probably not producing it to the same extent as adults. Dr. Faustman inquired about the cultural differences in the data shown for daily intake or blood levels of isoflavones in adults. Dr. Thayer stressed that the values depicted were drawn from several sources, with the goal of presenting an overview of the relative differences in exposure between infants and different populations of adults, i.e., omnivores, vegetarians or vegans, and adults consuming a traditional Asian diet. Dr. Faustman said it would be good to include infant data on equol where possible, to try to get an idea about cultural differences versus gut biome differences in terms of variability, and that there should be mention if the values from the Cao study might not represent the peak values in terms of time taken.

Dr. Cattley asked about interactions in mixtures of isoflavones. Dr. Thayer replied that this was one of the key data gaps identified. Dr. Faustman inquired about the inclusion of data cited as “personal communication” in the Draft Brief, and whether that was now acceptable under NTP standards. Dr. Bucher explained that in usage and exposure sections, there is somewhat more tolerance for unpublished, not rigorously peer-reviewed information, with such information on usage often coming from companies and manufacturers. Other types of data have a strict requirement for peer-review.

Dr. Eastman asked about evidence of local deconjugation of isoflavones due to sulfatases or glucuronidases in the target organs, thus escaping detection. Dr. Thayer replied that there was information for tissue levels of genistein. Dr. Eastman said such information about conjugated versus unconjugated forms would be useful.

Dr. Sherley asked for elaboration about references to “public concern” as used in the Draft Brief. Dr. Bucher replied that those mainly refer to public comments submitted to the expert panel, particularly several that described associations between SIF intake and potential problems. He said those comments were in the docket and available on the web. Dr. Thayer added that much of the public concern comes from more general concerns regarding phytoestrogens and exposures during critical periods of development.

Dr. Carney, the first lead discussant, said he was surprised that only two human exposure studies had made it through to full consideration by NTP and the expert panel, and wondered why an existing physiologically-based pharmacokinetic (PBPK) model for genistein did not appear to have been employed.

Dr. Eastmond, the second lead discussant, said a thorough job had been done in the draft document, but expressed the caveat that the upper end of the exposure range had not been adequately represented. For example, the Setchell 1997 *Lancet* article reported a wider range than that used in the Draft Brief. He urged a bit more caution, since in one million infants, a 95% confidence interval would leave out 25,000, a significant number. He pointed out that although total blood level of genistein is a good metric for making interspecies comparisons, the lack of measurements for aglycone, the bioactive form of genistein, has necessitated estimates, which can be unreliable. Dr. Eastmond questioned why the estimated daily intakes of isoflavones differed between those presented in the Setchell paper and those in the Draft Brief. Dr. Thayer explained the discrepancy was based on different assumptions in body weight of the infants (the NTP used standard EPA default values for infant body weight).

Dr. Faustman, third lead discussant, said the Draft Brief described the potential variability in average blood-based levels of isoflavones, genistein, and daidzein in infants and adults following a variety of dietary conditions. It was significant that comparisons across diets in adults, in various cultural diets, and with cow formula and human breast milk were made. This is helpful and provided strong support for the up to two orders of magnitude higher levels of genistein that could occur with SIF exposures. She requested that cited personal communications with NIEHS scientists be provided to the BSC in the future. A good job was done reviewing exposures, but she expressed surprise at how the estimates were used. She considered episodic, mixed exposures more reflective of actual exposure patterns in human populations; however epidemiology studies of less than 100% SIF exposures were dismissed as having no utility. She suggested more exposure analysis for these studies, and adding a discussion on how these studies could have been analyzed. She noted a lack of data on equol and information on PBPK modeling.

Ms. Rudel, the fourth lead discussant, said it was important that there were blood levels for infants in the United States provided, as points of comparison with animal studies. She concurred with Dr. Eastmond’s concerns about the high end of infant genistein exposure not being well characterized in the data considered, but felt that the uncertainty about the effects of mixtures of isoflavones versus a single protein is

perhaps more important. She agreed with the conclusion in the Draft Brief that oral versus injection dosing in neonatal rodents results in comparable blood profiles.

Dr. Tracie Bunton, the fifth lead discussant, felt that the exposure data were comprehensive and well documented, and that NTP had done due diligence in presenting the information that was available.

G. Weight of Evidence Conclusions for Adverse Effects on Development Based on Human Studies

Dr. Thayer presented the weight of evidence conclusions regarding adverse developmental effects in humans (1) *insufficient evidence* for a conclusion regarding developmental toxicity, and (2) *some evidence of no adverse effects* on growth in healthy, full-term infants. The human studies focused on studies of infants fed SIF. Most of the studies were considered of no utility; only 28 were considered of "limited' utility due to Inadequate sample size, changes in feeding methods, short-duration of follow-up, no validation of exposure to SIF, and inadequate consideration of potential confounding variables. The expert panel found "insufficient" evidence to reach a conclusion on reproductive endpoints, based on three studies of "limited" utility. Dr. Thayer described two ongoing prospective studies, the Arkansas Children's Nutrition Center study and the NIEHS Infant Feeding and Early Development (IFED) study, which may address some of the identified data gaps.

H. BSC Questions and Discussion

Dr. Eastmond asked whether some of the issues under consideration might be related to conjugation profiles due to infant metabolism, which until the age of approximately six months is quite low, citing the reports of hypothyroidism as potentially supporting evidence for the idea. Dr. Birnbaum replied that it is quite difficult to get that kind of information, including ethical issues related to taking blood samples from children. Dr. Eastmond noted that it would be possible in this case to acquire urine levels instead, looking for conjugated proteins. Ms. Rudel pointed out that in at least one study there was no correlation between urine and blood levels of isoflavones.

Dr. Faustman expressed concern about the weight of evidence slide, which she found confusing and hard to understand in light of convention on discussions of developmental toxicity (i.e., we include weight, malformation, viability and functional indications together as a marker of developmental toxicity). She felt that perhaps the endpoints should not have been split as they were and asked whether there was process discussion by the CERHR expert panel on this particular treatment. Dr. Thayer replied that the expert panel split the endpoints in order to be true to the AAP guidelines, which refer to adequate growth with SIF usage. Responding to a question from Ms. Rudel, Dr. Thayer elaborated on the panel's process in arriving at these particular conclusions and how they were presented. Dr. Carney said he felt that the color scheme made the weight of evidence conclusions resemble the levels of concern conclusions, and that the distinction between the two would be lost by a general audience. Thus, at the end of the document, with its "minimal concern" conclusion, it appears that the findings do not line up. He recommended only doing one such chart,

at the end, to avoid confusion. Dr. Thayer appreciated the feedback on the format of the document.

Dr. Eastmond expressed concern about the apparent use of a gradation of colors, suggesting the gradation toward less concern might be more effective toward green, versus the current blue scheme. Dr. Birnbaum pointed out that care must be taken in use of color, due to many color-blind people in the population.

Dr. Carney reiterated his concerns about using the same graphic for weight of evidence and levels of concern, and both Dr. Bunton and he questioned use of the word "possibly." Dr. Eastmond said he liked the general approach, and that it conveys a great deal of information simply.

Dr. Faustman lauded the authors for compiling and analyzing a tremendous number of studies for the report and subsequent brief. She provided suggestions for improving the brief (1) pull forward a summary table for the animal experiments similar to the summary tables 1 and 2 for exposures, (2) be more consistent in the discussion of statistics in the studies, (3) provide power calculations for the epidemiology studies, (4) do not dismiss the large body of animal research, (5) focus on the quality and design of studies rather than the number of studies, (6) include more discussion of integrated signals, (7) include comparisons such as a list of estrogenic compounds and total estrogenicity of all agents within the formulas, (8) provide the estrogen level for human breast milk to allow comparisons on the exposure level with the biological effects level. She was critical of Figure 2 for listing growth versus developmental toxicity since the assessment of growth is a part of the determination of development. The considerations of equol production were useful, as were the exposure comparisons for cow milk formulations and breast milk formulations for the isoflavone comparisons.

Ms. Rudell said typically she gives more weight to the animal studies in these assessments, but in this case the human studies are important. She postulated that if infants were being exposed to pure genistein, there would not be extensive discussion about the possibility of adverse effects, due to the relatively clear evidence of estrogenic responses in animal studies. However, the situation is more complex in infants because SIF is mixtures of compounds. She said she focused on how strong the human studies are in terms of being reassuring or raising concerns, but the studies are small and particularly underpowered for rare effects. Thus, she agreed with the statement of insufficient evidence for a conclusion.

I. Weight of Evidence Conclusions for Adverse Effects on Development Based on Laboratory Animal Studies

Dr. Thayer presented the CERHR expert panel's weight of evidence conclusions of (1) *clear evidence of adverse effects* for genistein and (2) *insufficient evidence* for a conclusion on adverse effects in laboratory animal experiments related to SIF, soy diet, soy protein isolate, mixtures of soy isoflavones, daidzein, glycitein, or equol. There were very few studies of SIF, and life stage at exposure was a major factor considered by the expert panel in determining study utility. Two co-twin studies (Sharpe 2002; Tan 2006), in which marmosets were fed SIF, demonstrated plasma testosterone and

testicular effects of SIF, with no clear effects on fertility. Genistein treatment of mice resulted in reduced fertility, multioocyte follicles, and abnormal estrous cyclicity. The NTP multigenerational rat study showed decreased litter size, decreased body weight, acceleration of vaginal opening, altered estrous cyclicity, and male mammary gland hyperplasia. Some limitations of the SIF animal studies are possible impacts from other non-isoflavone ingredients in SIF and interactions between genistein and other isoflavones.

J. BSC Questions and Discussion

Dr. Carney questioned the lack of attention to the porcine model in the Draft Brief and whether NTP and the expert panel had examined porcine studies and found them lacking, or whether they disagreed about the utility of the model itself, which public commenters had recommended. He also felt that use of the term “aglycone” should be clarified and consistent, in that there are two ways for that state to occur – when genistein is not bound to sugar, or not glucuronidated. He was at first skeptical about the subcutaneous dosing studies, questioning how they could be relevant to humans, but saw that the dosing was not a great deal more than would be found in an internal dose, and accepted the relevance of the data. In response, Dr. Thayer cited some issues regarding the utility of the swine model. Quoting from a public comment to the expert panel by Dr. Hans Stein, Associate Professor of swine nutrition at the University of Illinois, she said initially newborn pigs are lactating, and then later should only be fed a diet partially consisting of soy protein. Further, there have been no safety assessments of soy isoflavones in diets fed to swine. Thus, utility of the existing livestock literature is limited. Also, utility of swine as a research model is limited by lack of knowledge about equol production early in life. Dr. Carney reiterated that that he thought the swine literature might still be useful to assess.

Dr. Eastmond generally agreed with the conclusions. He felt that the livestock studies have some weaknesses that render them less useful than they might first appear to be.

Dr. Faustman said it would have been advisable to pull forward some groupings of the important findings in the animal studies, as had been done for the epidemiology studies in the brief. This lack serves to de-emphasize the animal studies. She said she was surprised by the expert panel’s tendency to dismiss the large body of animal research in this area. She found some of the data shown in the presentation to be significant and recommended it to be captured more fully in the Draft Brief, particularly integrated kinetic and health endpoint assessments. The variety of elements present in the conclusions shows that the issue is complex, beyond simply exposure to SIF itself. She found the isolated isoflavone animal studies to be significant, and combined with the kinetic studies, caused her concern, whereas the Draft Brief tended to dismiss those studies.

Ms. Rudel thought perhaps a higher level of concern was warranted, since the infant studies have shown genistein exposure levels equivalent to those in animal studies in which adverse effects have been documented. She remarked that the marmoset studies appeared not to show estrogenic effects of soy protein exposures and she agreed that more consideration of the agricultural studies would be useful. Dr.

Faustman pointed out that those were studies only in males, but that studies in females showed clear estrogenic effects. Ms. Rudel commented that those were genistein studies, and that with genistein there is clear estrogenation, but she didn't see that with any of the soy protein-only studies. Dr. Thayer again mentioned that the marmoset studies were only in males. Ms. Rudel said she was questioning whether soy protein isolate or SIF would engender an estrogenic response, and whether that has been seen in any of the studies considered by the expert panel, particularly the marmoset studies. In reference to the marmoset studies, Dr. Thayer agreed with an earlier statement by Dr. Carney that the testicular weight in the animals was more indicative of a thyroid than a potential estrogenic response.

K. Draft NTP Level of Concern Conclusion for Soy Infant Formula

Dr. Thayer presented the draft NTP level of concern conclusion for SIF. She noted that the answer to the question, *Can SIF or its Isoflavone Contents Adversely Affect Human Development?* was "possibly." This was based on clear evidence of adverse effects of genistein in laboratory animals and similarity in blood levels of genistein in infants fed SIF to laboratory animals treated with dose levels of genistein or genistin that caused adverse effects. The NTP concurs with the conclusion reached by the CERHR Expert Panel on SIF—"that there is *minimal concern* for adverse effects on development in infants who consume SIF."

L. BSC Discussion

Dr. Bunton agreed with the minimal level of concern based upon the comprehensive information provided. She agreed with previous comments questioning use of the word "possibly," stating that the term had a greater impact than seemed appropriate given the ultimate finding of a minimal level of concern, thereby creating confusion. She recommended that NTP review the language used for future briefs, or even this one.

Dr. Carney recommended that "possibly" just be deleted; in public communication, simpler is better and there should be just one bottom line message. Regarding the minimal level of concern conclusion, he said if this were an industrial chemical under consideration, given the data on hand, the conclusion would probably be higher on the level of concern scale, perhaps to "some" or even higher. The extensive history of human and livestock exposures to this substance (although that record is scientifically imperfect) should serve as "a reality check," and "minimal concern" is probably the right answer. He suggested it might be effective to show the entire range of exposure data as one box plot toward the end of the document, with one column for animal data and one for human, so that the overlap would be visually apparent.

Dr. Eastmond felt that use of the word "possibly" seemed reasonable given NTP's historical use of that term. Overall, he had been concerned about the similar exposure levels in infants and in lab animal experiments, where adverse effects were documented. But that given the huge history of use of SIF in the real world, with very little apparent adverse impact, he was ultimately comfortable with the conclusion of "minimal concern." His impression of the Draft Brief was that the negative studies were not focused on, but the positive studies received much more attention, leaving perhaps

a false impression that there was more evidence of effects than is actually warranted. He recommended adding summaries of key messages to help direct the reader.

Dr. Faustman said she could not concur with this section of the document. She agreed with Dr. Ruth Edsel's opinion on page 726 of the Expert Panel, i.e., that "minimal concern" was not high enough in reviewing this information. The collective signal from the animal studies that tested individual isoflavones is a strong indication for a potential for human health effects following exposure to SIF that contain high levels of these agents. This is given within the context of the minimum utility of the human epidemiology studies to identify the types of endpoints that were seen in animal studies.

She suggested stopping the document with a narrative about levels of exposure overlapping and exceeding by multiple orders of magnitude the exposure to components of soy that can cause serious developmental changes in animal models. The section 4.4, Overall Conclusions, does a good job of setting the type of ending for the Draft Brief. She said her comments consider the AAP advice about minimal reasons for using SIF given the potential magnitude of adverse effects from isoflavones. She advised CERHR to raise the potential for serious health impacts. Despite the many uncertainties and acknowledged recognition of the complexity of dietary components, the significance of potential impacts across a lifespan of exposed infants would merit a significantly higher level of concern.

Ms. Rudel said she disagreed with the "possibly" conclusion, given the "clear evidence of adverse effects of genistein in laboratory animals." Given the similarity in genistein blood levels between human infants fed SIF and lab animals treated with genistein or genistin, the more appropriate answer would be "probably" or even "yes." Thus, she also recommended raising the level of concern to "some concern" or even higher, based on the genistein data. She said further research is needed to concentrate on extrapolating from pure genistein data to reach conclusions on SIF itself, whether it is adverse or perhaps even beneficial.

Dr. Sherley disagreed with conclusions mentioned by his colleagues, stating the conclusions should have been "probably not" (as opposed to "possibly") and "negligible" (as opposed to "minimal"). He found the public commentary to be compelling, and felt that the BSC and NTP were perhaps being too formulaic in their analysis, and placing too much emphasis on a few animal studies. The comparisons between human and animal exposure data are not valid or appropriate. There is a biological explanation for why the rodent and human studies can appear to be different due to know metabolic differences in the way these compounds are handled. He was particularly compelled by the history of 25 million human exposures with no evidence of adverse effects. He said, in this case, the cost of the current rating should be part of the analysis.

Dr. Toraason also perceived a mismatch in the Draft Brief between the report of clear evidence of adverse effects in the animal studies and the conclusion of minimal concern. Ms. Rudel added that data on the differences in estrogenicity between genistein, SIF, and other forms of soy protein were important and should be included in more detail in the document.

Dr. Faustman asked for more detail about the power (or lack thereof) of the epidemiologic studies looking at reproductive endpoints. Dr. Thayer responded that for the most part that information was not available. Dr. Faustman said it would have been good to have some of the institute's epidemiologists review the studies to examine the data regarding reproductive endpoints. Dr. Birnbaum asked NIEHS epidemiologist Dr. Walter Rogan, who was present for the discussion, to comment. Dr. Rogan confirmed Dr. Faustman's assertion that for the most part the groups in the human studies were too small to shed light on the reproductive endpoints of interest, and that that is why there was little reference in the Draft Brief. He imagined clinicians would be surprised if there were strong action taken on SIF given the product's 50-60 year track record in wide usage with no adverse effects detected in that time.

Dr. Bunton moved that the science cited in the draft NTP Brief on SIF supports the conclusion of *minimal concern* for adverse effects on development in infants who consume SIF. Dr. Carney seconded the motion. The vote was in favor of the motion with 7 yes votes, 3 no votes, and 0 abstentions. Dr. Sherley said his opposition was as stated previously, that the conclusion should be "negligible concern." Dr. Faustman said she felt that the level of "minimal concern" did not accurately reflect the potential for adverse health effects, unless further studies are done. Ms. Rudel stated that in her opinion "minimal concern" understates the level of concern, and there should be more concern based on the animal data and pending new studies.

IV. NTP Testing Program: Proposed Research Concept for Isoflavones in Soy Infant Formula

A. Presentation of Proposed Research Concept

Dr. Kembra Howdeshell reminded the BSC of the various types of isoflavones in SIF and their *in vitro* estrogenic potency. On March 16, 2010, NTP released a draft NTP Brief on SIF expressing "minimal concern" for adverse effects on human development. The draft NTP conclusion was based on clear evidence for adverse effects of genistein on reproductive development and function in female rats and mice manifested as (1) accelerated puberty (i.e., decreased age at vaginal opening), (2) abnormal estrous cyclicity, (3) cellular changes to the female reproductive tract, and (4) decreased fecundity (i.e., decreased fertility, implants, and litter size). Blood levels in human infants fed SIF can exceed those measured in neonatal or weanling rodents following treatment with genistein at dose levels causing adverse effects in the rodents.

Dr. Howdeshell presented some key data gaps in the animal literature. An important issue is the contribution of equol to the *in vivo* estrogenic potency of daidzein. The i*n vitro* estrogenic potency of equol is similar to genistein. Approximately 30-50% of adult humans, and even fewer infants, are considered "equol producers." Adult rodents and non-human primates produce equol but there is no information on rodent pups. It has been suggested that the estrogenicity of equol *in vivo* is less than predicted based on *in vitro* studies. This has been attributed to significant conjugation of equol as measured in blood. Dr. Dan Doerge, FDA/NCTR, in a personal communication, has stated that equol has been detected in infant and adult rhesus monkeys treated with daidzein, but < 0.3% was detected in unconjugated form.

The majority of studies have evaluated the effects of only one isoflavone, genistein; however, other soy isoflavones may influence the action of genistein by binding to the estrogen receptor. Additionally, non-isoflavone components (e.g. corn syrup, vegetable oils, sugar, vitamins, minerals and other nutrients) may affect the absorption or biological activity of the isoflavone components. Contaminants (e.g., phytates or protease inhibitors that have antitrypsin, antichymotrypsin, and antielastin properties) are also present. It is difficult to study the nonisoflavone components in isolation, so there is a need to study SIF *in toto* to see how they interact

Dr. Howdeshell described the limited number of period of lactation-only studies with SIF or soy isoflavone mixtures, including the marmoset twin studies. Many studies of soy diet, soy protein isolate, or mixtures of soy isoflavones included treatment outside the period of lactation, thus were also of limited utility. The period of lactation-only studies of soy diet, soy protein isolate, or mixtures of soy isoflavones provided "insufficient" evidence to reach a conclusion in the draft NTP Brief on SIF.

Dr. Howdeshell described the specific aims of the proposed research concept, which will use lactation-only, oral dosing of mouse or rat pups:

(1) Identify the developmental profile of daidzein metabolism to equol during development. There will be a preliminary study to determine blood levels of daidzein, followed by PK studies at different ages during the period of lactation following administration of daidzin to mouse pups.

(2) Evaluate how individual soy isoflavones act in combination on an estrogen responsive endpoint. There will be uterotrophic assays of soy isoflavones in neonatal mice and an evaluation for evidence of dose-addition, response-addition, antagonism, or synergism. If antagonism is detected, further mixture experiments would evaluate whether daidzin or glycitin inhibit the action of genistin.

(3) Evaluate the feasibility of administering SIF to mouse and/or rat pups beginning on PND1. If that is possible, NTP will conduct reproductive, development, and fertility studies with SIF and do PK studies measuring isoflavones. If administering SIF is not feasible, there will be an attempt to administer a mixture of isoflavones (in the ratio they are present in SIF) in SIF vehicle and to do companion PK studies measuring isoflavones.

B. BSC Questions and Discussion

Dr. Eastmond asked Dr. Howdeshell whether the plan to use glycosylated isoflavones was intended to more specifically mimic SIF exposures, which Dr. Howdeshell confirmed. They discussed the possibility of conducting interaction studies in cell culture, and Dr. Howdeshell said she was considering collaborations with NTP and NIEHS scientists to do *in vitro* studies to assess aglycone (non-sugar bound and unconjugated) isoflavones.

Dr. Bunton inquired whether estrogen receptor binding studies would or could be conducted prior to the uterotropic assays, so that those assays could be eliminated

altogether. Dr. Howdeshell replied that some existing studies along those lines had been looked at in the preparation of the Draft Brief, but she doubted such studies could be used in lieu of the uterotropic assays, based upon the need for dose selection information for the individual isoflavones as the basis for analyzing mixture effects.

Dr. Sherley questioned the emphasis in the proposed program on matching the feeding schedule, given the many other differences between the early development of human infants and rodents. Dr. Howdeshell responded that in the case of the mouse pups, very little isoflavone content is passed through the milk during lactation, so the oral dosing was chosen to most accurately model how human infants are exposed. She acknowledged that differences in early development are a limitation of the animal model.

Dr. Carney, the first lead discussant, felt the rationale was very clear and aligned closely with data gaps identified in the day's discussions. He said the program did fit the NTP's mission, particularly given widespread exposure to infants and small children, populations that are always of great concern. The NTP has designated SIF as being of minimal concern, and further study is unlikely to significantly advance scientific knowledge, but study of endocrine disrupting chemicals is likely to expand greatly in coming years. The body of knowledge about soy and the tremendous amount of human exposure could make it an ideal model. Regarding the scope of the program, Dr. Carney said it would be difficult to elicit any change in the level of concern that might emerge from the additional studies. He questioned whether there would be a great deal of value in more animal data, when the important questions revolve around human data. He suggested the answer is somewhere in the middle, with a place for both types of research. He discouraged initiation of a comprehensive animal testing program as with other chemicals, but favored a program highly targeted to the key areas that would translate into improved risk assessment. Dr. Carney strongly supported lactation-only exposure studies using test material that most closely resembles SIF. To get the most return on the research investment, it would be best to focus on the most sensitive effects of SIF that drive the boundary between human exposures and animal internal exposures. He recommended not doing studies in both mice and rats, and that the researchers should pick one or the other, probably the rat. He added that many of the estrogenic compounds under consideration are most precisely referred to as selective estrogen receptor modulators. This becomes an item of concern when assessing mixtures. With the many elements involved, it is unlikely the program would be able to arrive at a universal conclusion about SIF, so the program might be intellectually interesting, but probably would not change science a great deal. He endorsed the study of equol production in the program. With regard to the program's listed specific aims, he gave #1 (assessment of equol production during mouse development) high priority, #2 (uterotropic assay to assess estrogenicity of isoflavone mixtures) very low priority, and advised that, #3 the reproductive development and fertility be one study or the other, not both (i.e., one rodent model).

Regarding specific aim #2, Dr. Howdeshell said she had experience doing mixture studies. She referenced a phthalate review done by the National Academy of Sciences, and its recommendation to assess additional antiandrogenic compounds due to their

action on a common target tissue. She said it would be interesting to determine whether there would be a larger effect in mixtures based on a dose-additive effect. Dr. Carney agreed that the study would be interesting, but because of the limited applicability domain, he questioned the public health value.

Dr. Faustman, the second lead discussant, endorsed the idea of starting the proposed research with PK studies, to be followed by experiments to confirm the relative estrogenicity of the various isoflavones contained in SIF, as well as to characterize the potential interaction of phytoestrogenic compounds in formula mixtures. She suggested modeling and direct studies of life stage-specific changes in kinetic metabolism and conjugation, followed by uterotrophic assays. She asked how these experiments might change the BSC's conclusion, given the fact that the current decision reflects the fact that there is clear evidence of adverse effects in animal studies, but the large body of human exposure experience appears to contain no such signal. She recommended more assessment and evaluation of endpoints such as mammary gland and nipple development. She felt the data that are already available should be mined more effectively, and that the study should be more broad and inclusive, assessing the impact of soy product exposures at more life stages than infancy alone since the document mentioned soy cereal use early in life. She found little remaining reasons for anyone to be feeding infants SIF.

Dr. Looney, the third lead discussant, said the rationale for the proposed research program is clearly described and the data gaps and research needs identified are well articulated. The proposed research directed toward determining the effects of lactation-only treatment with a mixture of isoflavones is directly relevant. He urged that great care be taken in designing the experiments and analyzing the data, particularly in studies of mixtures, with such studies often being underpowered due to flawed design. The limit of detection for equol is another important issue, he said, and the proposed research should help determine what is appropriate, which would be of value with other studies. He expressed less enthusiasm about the potential contribution of these experiments to the overall information base on potentially hazardous substances. He said that although the gaps in this area have been identified, it is not clear what the implications will be for public health in general, or infant feeding specifically, once those gaps have been filled. He said he would assign this research concept a low priority.

Mr. Janzen, the fourth lead discussant, thought the study program was well thought out, and was pleased to see the re-arrangement of the specific aims compared to the initial document. On clarity and validity of the program, he suggested that many of the questions about how these mixtures interact could be answered very simply with *in vitro*, high-throughput experiments. He was concerned that many of the confounding issues that had ruled out other studies from being considered by the CERHR expert panel were still present in this program, particularly the problem of extrapolating equol production in the rodent population to that of the human population, when that question is still outstanding. He felt that the program has a great deal of merit, but that the study needs to be done very carefully to address the questions. He questioned the possibility of developing a biomarker for the metabolism that occurs in the gut flora. He felt that the scope of the program seemed appropriate, and would assign it a fairly high priority.

Dr. Howdeshell said modeling and assessing *in vitro* data have been under discussion by her group. She mentioned that specific aims #1 and #2 would be conducted in-house at NIEHS, with #3 taking place at a contract research laboratory. She said regarding daidzein metabolism to equol, it would be necessary to examine that *in vivo* as opposed to cell culture. She also reiterated her experience in working with mixtures, and the availability of expertise from which to draw.

Dr. Eastmond about some of the other animal models CERHR might have been considering. She responded that they had also been considering rabbits, guinea pigs, and the pig model, in addition to rodents.

Dr. Faustman asked whether there had been any discussion of a collective vision for the research plan, beyond questions restricted to SIF. Dr. Bucher replied that it depended on this meeting's outcome, since the draft brief on SIF deals with the highest exposed group at the most sensitive age range. It would be difficult to justify a research endeavor on soy exposure in adults. Dr. Faustman asked about concern for teenagers; there are other soy exposures beyond SIF. Dr. Thayer said the composition of isoflavones is completely different in supplements and foods compared to SIF, so the experimental approach would be very different. Dr. Faustman replied that this was a great opportunity to address a broader question than just SIF. Dr. Birnbaum commented that many different groups are looking at those very questions, including the potential benefits of soy nutrition in adults, but that she did not want to confound the discussion about early life stage exposure to SIF with a separate evaluation.

Dr. Eastmond commented that the proposed aims appeared to be an outgrowth of the draft brief. He said he saw a lot of value for doing the proposed studies, because they would help to justify the overall conclusion of minimal concern about SIF exposures. He agreed that young children are consuming considerable amounts of soy products. He strongly agreed with earlier comments about the wisdom of conducting receptor binding *in vitro* screens before doing *in vivo* studies, not only to reduce animal use, but also to specifically target individual combinations of chemicals.

Dr. Cattley agreed that it would be wise to substitute one of the rodent models with another model, such as the pig. If experiments are restricted to rodents, there is still the extrapolation problem previously discussed. Dr. Eastmond said that much data on later life exposures already available from pig studies, and that perhaps it would not be necessary to duplicate it. Dr. Thayer outlined some potential problems with that approach.

Ms. Rudell commented that the research program follows her reaction to the Draft Brief in that she thought there is some concern about SIF, based on the animal studies. There is a suggestion that SIF as a mixture somehow does not have as strong an estrogenic effect; that it somehow mitigates the estrogenic effect of the genistein it contains. With that in mind, she wondered what studies might serve to raise or lower her level of concern. The human studies already underway might do so, she said, and she was curious about what studies might influence her fellow BSC members to raise or

lower their levels of concern. She suggested evaluating SIF in addition to individual soy isoflavones and combinations in specific aim #2.

Dr. Novak summarized the discussion, citing a degree of enthusiasm for pursuing the studies; specific aim #1 (assessment of equol production during mouse development) was ranked high.

V. Technical Reports Review Subcommittee Report from the November 19, 2009 Meeting

A. Presentation of Subcommittee Report

Dr. Cattley chaired the report on the Technical Reports Review Subcommittee ("the Subcommittee") meeting. Dr. Novak, chair of the Subcommittee, presented the recommendations from the November 19, 2009 meeting on behalf of the Subcommittee.

The Subcommittee reviewed the findings and conclusions from the studies of 1-bromopropane, ginseng, pulegone, milk thistle extract, bis(2-chloroethoxy)methane, and diethylamine that all used conventional F344 rat and B6C3F$_1$ mouse models. Voting totals differed due to several members' absence during parts of the meeting and/or recusal from participating in discussions due to potential conflicts of interest.

- The Subcommittee accepted unanimously (9 yes, 0 no, 0 abstentions) the conclusions, *some evidence of carcinogenic activity* of 1-bromopropane in male rats*, clear evidence of carcinogenic activity* in female rats, *no evidence of carcinogenic activity* in male mice, and *clear evidence of carcinogenic activity* in female mice. The Subcommittee recommended that pancreatic islet adenoma and carcinoma (combined) be added to the conclusion in male rats and that the origin of skin neoplasms (epithelial) in male and female rats as well as the types of neoplasms (keratoacanthoma, squamous cell carcinoma and basal cell neoplasm) in male rats be added to the conclusions.
- The Subcommittee accepted (6 yes, 4 no, 0 abstentions) the conclusions as written, *no evidence of carcinogenic activity* of ginseng in male and female rats or mice.
- The Subcommittee accepted (6 yes, 4 no, 0 abstentions) the conclusions, *no evidence of carcinogenic activity* of pulegone in male rats, and *clear evidence of carcinogenic activity* in male and female mice. The Subcommittee recommended the conclusion of *clear evidence of carcinogenic activity* in female rats based on increased incidences of urinary bladder neoplasms. The Subcommittee recommended that the specific types of liver neoplasms in mice that increased with treatment be reported in the conclusion.
- The Subcommittee accepted unanimously (10 yes, 0 no, 0 abstentions) the conclusions as written, *no evidence of carcinogenic activity* of milk thistle extract in male and female rats or mice.
- The Subcommittee accepted unanimously (7 yes, 0 no, 0 abstentions) the conclusions as written, *no evidence of carcinogenic activity* of bis(2-chloroethoxy)methane in male or female rats or mice.
- The Subcommittee accepted unanimously (8 yes, 0 no, 0 abstentions) the conclusions, *no evidence of carcinogenic activity* of diethylamine in male or female

rats or mice. The Subcommittee recommended that the nonneoplastic lesions in the cornea of male rats be added to the conclusions.

B. BSC Discussion

Dr. Faustman moved to accept the Subcommittee report as presented and Dr. Eastmond seconded the motion. The BSC voted unanimously in favor of the motion with 9 yes votes, 0 no votes, and no abstentions.

VI. CERHR Proposed Approach for the Evaluation of Low-Level Lead

A. Presentation of Proposed Approach

Dr. Andrew Rooney presented the proposed CERHR approach for the evaluation of low-level lead. The charge to the BSC was to review and comment on the proposed approach for the development of the NTP evaluation of low-level lead. Specific comments were requested for the development of the draft NTP Monograph for Low-Level Lead, the proposed use of external scientists, and the involvement of the public. Dr. Rooney also requested any other comments CERHR staff should consider in developing the evaluation project.

The evaluation of low-level lead was nominated by Dr. Elizabeth Whelan of NIOSH and was approved by the BSC by a unanimous vote at the December 6, 2007 meeting. The OSHA occupational exposure limit allows blood lead levels of 40 µg/dL, including worker populations that include women of childbearing age. However, there is epidemiological evidence of health effects below 10 µg/dL, indicating a disconnection between health effects and allowable exposure limits. The scope of the evaluation will focus on health effects < 10 µg/dL where there is greater uncertainty. The CDC's definition of elevated blood lead level has been ≥ 10 µg/dL since 1991 for children. Health effects are well established at higher levels. CERHR has expanded the scope beyond effects on reproduction and development to include cardiovascular and renal effects and effects of exposure prenatally and during childhood, adolescence, and adulthood.

The evaluation is designed to address the overarching question: What is the weight of evidence for adverse health effects associated with blood lead levels < 10 µg/dL? The specific questions to develop the weight of evidence evaluation are (1) what health effect(s) are associated with blood lead levels < 10 µg/dL, (2) at which life stages – prenatal, childhood, adolescence, or adulthood – is the effect identified, (3) what is the blood lead level associated with the specific health effects, and (4) are there additional biomarkers of exposure associated with effects (e.g., bone lead), and (5) what is the relationship between these biomarkers and blood lead levels. The biomarker question acknowledges that other exposure metrics are available and that blood lead levels may reflect current exposure, whereas bone lead may reflect cumulative exposure.

Putting the low-level lead evaluation in the context of the CERHR evaluation process, Dr. Rooney explained that the nomination and selection were completed previously; the proposed approach is being presented to the BSC now. The preparation of the Draft NTP Monograph by CERHR staff will include a literature review of the

epidemiological evidence that is supported by animal data and the development of weight of evidence conclusions. CERHR anticipates that the weight of evidence conclusions will be based primarily on epidemiological evidence. Scientific input will be sought through issuance of a Federal Register notice that requests current and ongoing studies on health effects of low-level lead. Technical advisors will be engaged to comment on issues of scientific complexity, adequacy of the literature review, and overall presentation of a pre-public release version of the draft Monograph. As before, interagency review and public comments will be solicited, and a formal peer review of the draft monograph conducted. Peer review will consist of an *ad hoc* expert panel convened under Federal Advisory Committee Act regulations. The expert panel meeting will be open to the public; a BSC member will attend and report back to the BSC. The expert panel will be charged to determine whether the science cited in the draft NTP Monograph on Low-Level Lead is technically correct, clearly state, and supports the NTP's conclusions. CERHR will finalize the draft monograph by considering the public and panel comments. As a final step, the NTP director will present the NTP monograph to the NTP Executive Committee followed by its release to the public.

CERHR anticipates that the NTP Monograph on Low-Level Lead will (1) provide an evaluation of the epidemiological data on health effects associated with blood lead levels < 10 µg/dL, (2) provide clarity for health effects of lead at lower exposure levels, (3) identify data gaps for evaluating the heath effects associated with lead at blood lead levels < 10 µg/dL, and (4) develop research recommendations based on data gaps.

B. BSC Questions and Discussion

Dr. Sherley requested an update since the initial nomination of lead. Dr. Rooney said the EPA completed the Lead Air Quality Criteria Document in 2006 and Agency for Toxic Substances and Disease Registry (ATSDR) completed its review of lead in 2007. CDC and the NIOSH Adult Blood Lead Epidemiology and Surveillance (ABLES) program lowered the adult reporting level to 10 µg/dl in 2009 and 2010. New publications have provided stronger evidence for health effects, especially on the cardiovascular system and developing nervous system, at and below 10 µg/dl. Additional studies have demonstrated altered onset of maturation and puberty associated with lead exposure. The CDC's Advisory Committee on Childhood Lead Poisoning and Prevention is developing a document to provide advice to physicians on exposure of pregnant women to lead. Dr. Rooney clarified to Dr. Sherley that the original nomination was to evaluate effects of lead below 40 µg/dL. Additional data since the nomination have added to the strength of the data demonstrating health effects below 40 µg/dL. CERHR is narrowing the focus of the evaluation to lead levels at and below 10 µg/dL and taking advantage of existing documents to cover higher blood lead levels. Dr. Thayer confirmed that OSHA's occupational exposure limit level is still at 40 µg/dL and the reduction in the CDC reporting level for adults did not change the occupational exposure limit.

Dr. Toraason asked if cardiovascular effects would be assessed only during development or additionally during post development, which would expand the mission of CERHR. Dr. Rooney said the full range of exposures would be considered. Dr.

Birnbaum confirmed that the NTP is in the process of expanding the scope of CERHR beyond reproduction and development to better fulfill the mission of the NTP.

Dr. Cattley, the first lead discussant, considered the approach appropriate, including the use of technical advisors, the creation of a draft document, interagency review, and public peer review. He questioned how much CERHR could take advantage of the ATSDR lead document. Dr. Rooney said CERHR intends to make the best use of and build upon existing EPA and ATSDR documents. Dr. Cattley supported the scope and suggested focusing on exposures during early development and adolescence, which are very sensitive populations. He also supported reviewing bone lead and the need for finding a better marker for cumulative lead exposure.

Ms. Rudel, the second lead discussant, expressed support for the approach and considered it an important project.

Dr. Sherley, the third lead discussant, agreed that the approach was excellent and concurred that it is important to find a marker for cumulative lead exposure. He questioned the progression of the nomination and asked for the lowest blood lead levels CERHR would assess for adverse health effects. Dr. Rooney said the best metric for cumulative exposure is bone lead because bone is a repository for lead. Non-invasive techniques such as X-ray fluorescence are becoming more widely used to test bone lead levels. Data are increasingly available demonstrating the association between bone lead levels and health effects. Health effects of lead exposure <10 µg/dL include immunotoxicity, as shown in animal studies and some human studies, developmental neurotoxicity, and some hematological effects. Cardiovascular and renal effects have been demonstrated in adults at blood levels <10 µg/dL; effects from developmental exposure are less clear. Dr. Rooney said the CDC states that there is no safe level of lead and no threshold for exposure.

Dr. Faustman expressed support for CERHR assessing other effects of lead exposure because worker populations have demonstrated cardiovascular effects associated with lead exposure. She asked about dose-response relationships and the potential for linking low-dose effects with higher dose effects across doses and about using violence and criminal behavior as endpoints. Dr. Rooney said CERHR would be addressing low-dose effects, but also reviewing available evidence of the dose-response relationships. The literature on lead neurotoxicity covers a range of endpoints including hearing, behavior, IQ, and aggression.

VII. Conclusion and Adjournment

Dr. Birnbaum thanked the BSC for an intensive day of hard work evaluating a tremendous amount of information. Dr. Bucher added his thanks and said the NTP values the comments the BSC provides. The NTP will reassess the design of the SIF studies in light of the comments from the meeting.

Dr. Novak adjourned the meeting at 3:45 PM.